REMARKS

The present invention provides targeting methods that combine the ability to genetically encode a protein sequence, and specifically express that sequence within living cells, with the use of well characterized spectroscopic probes or other probes. The invention thus permits the use of a wide variety of fluorophores, as well as other spectroscopic probes, including nuclear magnetic resonance (NMR), positron emission tomography (PET), relaxation reagents, chromophores, and other reagents such as chemical cross linkers, caged compounds, enzymatic substrates, activators, and the like.

Responsive to the Examiner's objection to the specification regarding the abstract, enclosed herewith is the abstract on a separate sheet as required by 37 C.F.R. 1.72(b).

A. Rejection Under 35 U.S.C. § 112, Second Paragraph

The rejection of claims 11 and 13-15 under 35 U.S.C. § 112, second paragraph as allegedly being indefinite for failing to particularly point out and distinctly claim the subject matter which Applicant regards as the invention, is respectfully traversed. Applicant respectfully disagrees with the Examiner's assertion that there is allegedly no antecedent basis for the phrase "said cell" (as recited in claims 11 and 13-15) in claim 3, upon which claims 11 and 13-15 depend. Contrary to the Examiner's assertion, Applicant respectfully submits that proper antecedent basis exists for the subject phrase since claim 3 depends on claim 1, which recites "a cell". Thus, since claims 11 and 13-15 depend from claim 3, which in turn depends from claim 1, proper antecedent basis does indeed exist for the phrase "said cell". Accordingly, reconsideration and withdrawal of the rejection of claims 11 and 13-15 under 35 U.S.C. § 112, second paragraph, are respectfully requested.

B. Rejection under 35 U.S.C. § 112, First Paragraph (Enablement)

The rejection of claim 5 under 35 U.S.C. § 112, first paragraph as allegedly containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention, is respectfully traversed. Applicant respectfully disagrees with the Examiner's assertion that the specification allegedly does not teach one skilled in the art how to make and/or use the invention commensurate in scope with the subject matter of claim 5.

It is well-established that the claims of a patent application are presumptively enabled when the application is filed. Thus, the burden of demonstrating that the entire breadth and scope of the claims is allegedly not enabled falls on the Examiner. In this case, the Examiner has provided no evidence to call into question the enablement of claim 5. Accordingly, it is respectfully submitted that the Examiner has not met the burden of demonstrating non-enablement.

Contrary to the Examiner's assertion, the method of the present invention, as defined by claim 5, is not drawn to any and all single chain antibodies. Instead, the method as defined by claim 5 requires a single chain antibody having at least 30% sequence identity to SEQ. ID. NO. 1. In addition, the single chain antibody required by claim 5 is capable of recognizing PhOx. Thus, rather than being drawn to any and all single chain antibodies, those skilled in the art recognize that claim 5 is drawn to a well-defined set of antibodies.

Furthermore, SEQ. ID. NO. 1 is set forth in the specification as an exemplary single chain antibody. Those skilled in the art can readily use routine techniques to develop single chain antibodies that are related to, but different in primary sequence from SEQ ID NO:1, yet retain the ability to bind PhOx. This is especially true for antibody molecules, since the precise structure of such molecules and the effects of amino acid changes on the binding properties of such

molecules has been extensively studied. In addition, there is considerable teaching on amino acid substitutions that are conservative, and therefore, are far less likely to affect antibody binding properties. Thus, it is respectfully submitted that, at most, only routine experimentation is required to practice the invention commensurate in scope with claim 5. Accordingly, it is respectfully submitted that the rejection of claim 5 under 35 U.S.C. § 112, first paragraph, as allegedly lacking an enabling disclosure, is not properly applied. Accordingly, reconsideration and withdrawal of the rejection are respectfully requested.

C. **Rejection Under 35 U.S.C. 112, First Paragraph (Written Description)**

The rejection of claims 5 and 6 under 35 U.S.C. § 112, first paragraph, as allegedly containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor, at the time the application was filed, had possession of the claimed invention, is respectfully traversed.

As acknowledged by the Examiner, Applicant is in possession (i.e., Applicant has provided adequate written description) of a method employing the single chain antibody SEQ ID NO:1. However, Applicant respectfully disagrees with the Examiner's assertion that there is allegedly inadequate written description for any single chain antibody or any homologue of SEQ. ID. NO. 1. As set forth above, the present invention is not drawn to any and all single chain antibodies, but instead is drawn to a well-defined set of antibodies having a well-defined function.

Applicant respectfully submits that the specification as filed provides sufficient written description for claims 5 and 6. Many single chain antibodies are known in the art. Each of these antibodies by definition binds a ligand. Therefore, based on the specification as filed, including the demonstration that a single chain antibody that recognizes PhOx can be successfully employed in the methods of the present invention, one of ordinary skill would

recognize that many single chain antibodies can be used in the methods of the present invention. In other words, the characteristic of a single chain antibody necessary to be used in a method of the present invention (i.e. the ability to bind a ligand), is an inherent property of such an antibody. Therefore, it is respectfully submitted that the invention methods, as defined by claims 5 and 6, are adequately described by the specification as filed.

Furthermore, with respect to claims 5 and 6, the disclosure provides sufficient structural and functional information to meet the written description requirement of 35 U.S.C. 112, discussed in *Regents of the University of California v. Eli Lilly & Co.*, 119 F3d 1559, 1569 (Fed. Cir. 1997). The relevant portion of *Regents* involve claims related to vertebrate insulin cDNA and mammalian insulin cDNA, the structure of which is provided by nature. On the other hand, the methods of claims 5 and 6 relate to single chain antibodies in general, and the ability of such antibodies to bind a ligand. The Federal Circuit in *Regents* indicated that a written description of a chemical genus requires a precise structural definition, and is not satisfied solely by functional language, such as a "vertebrate insulin cDNA." *Regents,* at 1582. Unlike the nucleic acids at issue in *Regents* whose structures are defined by nature and were unknown as of the filing date of the patents at issue, single chain antibodies used in the methods of the present invention are well-known and described in the art. The particular specificity or binding properties of the single chain antibodies are not critical to the invention. All that is required is that the single chain antibodies bind a ligand, an inherent property of a single chain antibody.

Single chain antibodies with homology or substantial identity to SEQ ID NO:1 which bind PhOx, are not a genus of unknown structures that was defined by nature, as was the case for vertebrate insulin in the *Regents* case. Rather, those skilled in the art can readily determine whether a sequence has sufficient sequence identity to meet the claimed limitation, and retains the ability to bind PhOx. Therefore, single chain antibodies that are homologues or substantially identical to SEQ ID NO:1 are adequately described in the specification. Accordingly,

reconsideration and withdrawal of the rejection of claims 5 and 6 under 35 U.S.C. § 112, first paragraph, are respectfully requested.

D. Rejections Under 35 U.S.C. § 103(a)

The rejection of claims 1-4, 6, 11-14, 16, 17, 60, and 63-74 under 35 U.S.C. § 103(a), as allegedly being unpatentable over Chesnut, et. al. (U.S. Patent No. 6,017,754) in view of Haugland, et. al. (Handbook of Fluorescent Probes and Research Chemicals 6th edition, pages 13-15, 18-19 (1996)) and Kopia, et. al. (WO 93/11120), is respectfully traversed. As acknowledged by the Examiner (see Office Action mailed April 9, 2002, page 8, lines 4-7), Applicant's invention, as defined by claim 1, distinguishes over the primary reference (Chesnut) by requiring a method for localizing a probe comprising contacting a sample comprising a cell expressing a single chain antibody with a membrane permeant probe/ligand conjugate, the membrane permeant probe/ligand conjugate comprising a probe moiety, a ligand that can bind with the single chain antibody, and a linker moiety coupling the probe to the ligand.

Applicant respectfully submits that none of the cited references, either alone or in combination, suggest a method as defined, for example, by claim 1. To establish a *prima facie* case of obviousness there must be some suggestion or motivation in the prior art to make the claimed invention, there must be a reasonable expectation of success, and the prior art reference must teach or suggest all of the claim limitations. MPEP 2142; In re Vaeck, 947 F.2d 488, 20 USPQ2d, 1438 (Fed. Cir. 1991). The mere fact that references can be combined or modified does not render the resultant combination obvious, unless the prior art also suggests the desirability of the combination. MPEP 2143.01 citing In re Mills, 916 F.2d 680 (Fed. Cir. 1990). If the proposed modification of one prior art reference would render it unsatisfactory for its intended purpose, then there is no suggestion or motivation to make the proposed modification. MPEP2143.01 citing In re Gordan, 733 F.2d 900, 221 (Fed. Cir. 1984).

The cited references, Chesnut, Haugland, and Kopia et al., either singly or in combination, do not render obvious a method with all of the elements of the pending claims. That is, the combination of these references does not result in a membrane permeant conjugate for detecting a single chain antibody or a specific binding pair member expressed from a recombinant nucleic acid. Those skilled in the art recognize that the BSA moiety and the cell-separation means of the FITC-BSA-PhOx complexes discussed in Chesnut render the conjugates membrane impermeable.

Reliance on Haugland or Kopia fails to cure the deficiencies of Chesnut. Haugland merely describes an alternative fluorescent moiety, BIODIPY FL. Substitution of BIODIPY FL for FITC in Chesnut's conjugate clearly does not render the conjugate membrane permeable. Similarly, Kopia merely describes an aliphatic linker moiety. There is simply no expectation that incorporation of an aliphatic linking moiety into Chesnut's conjugates would render Chesnut's conjugates membrane permeable. Thus, it is respectfully submitted that the Examiner's combination of Chesnut with either Haugland or Kopia does not result in the conjugates employed in the present invention methods. Indeed, absent the teachings of the present specification, there is no motivation to combine the references in the manner set forth by the Examiner. Such hindsight use of Applicant's specification is respectfully submitted to be improper.

The rejection of claim 9 under 35 U.S.C. § 103(a), as allegedly being unpatentable over the cited references and further in view of Lauffer, et. al. (U.S. Patent No. 5,628,982), is respectfully traversed. Lauffer merely describes hydroxy-aryl metal chelating agents for use as NMR contrast agents. Those skilled in the art would readily acknowledge that the use of hydroxy-aryl metal chelating NMR contrast agents would not impart membrane permeability to the conjugates produced by the combination of Chesnut, Haugland, and Kopia. Accordingly, further reliance on Lauffer fails to cure this deficiency of the cited references.

The rejection of claim 10 under 35 U.S.C. § 103(a), as allegedly being unpatentable over the cited references and further in view of Green, et. al. (U.S. Patent No. 5,324,502), is respectfully traversed. Green merely describes gallium complexes of tri- and tetra-amines with optionally substituted salicylaldehydes for use as positron emission tomography (PET) imaging agents. Those skilled in the art would readily acknowledge that the use of such gallium agents would not impart membrane permeability to the conjugates produced by the combination of Chesnut, Haugland, and Kopia. Accordingly, further reliance on Green fails to cure this deficiency of the cited references.

The rejection of claim 15 under 35 U.S.C. § 103(a), as allegedly being unpatentable over the cited references and further in view of Rizzuto, et. al. (*Current Biology* 5(6):635-42 (1995)), is respectfully traversed. Rizzuto merely describes a conjugate containing green fluorescent protein (GFP) and further teaches adding a stimulus to the cell. GFP is used by Rizzuto for intracellular localization because it is expressed within the cell, not because it is membrane permeant. Large charged molecules such as proteins are not membrane permeant. Therefore, substituting GFP for FITC in the conjugates of Chesnut would result in a conjugate with 2 large charged proteins, BSA and GFP, which would render the conjugate even more membrane impermeant. Thus, with specific reference to claim 15, Rizzuto's teaching of a stimulus is respectfully submitted to be immaterial, since the combination of the cited references with Rizzuto could not result in a membrane permeable conjugate, as required by the present invention. Accordingly, further reliance on Rizzuto fails to cure this deficiency of the cited references.

The rejection of claim 18 under 35 U.S.C. § 103(a), as allegedly being unpatentable over the cited references and further in view of Youn, et. al. (Analytical Biochemistry, 232:24-30, 1995), is respectfully traversed. Like Haugland, Youn merely describes an alternative fluorescent moiety, $[Ru(bpy)_2(phen\text{-}ITC)]^{2+}$. Those skilled in the art readily recognize that

substitution of $[Ru(bpy)_2(phen\text{-}ITC)]^{2+}$ for FITC in Chesnut's conjugate clearly does not render the conjugate membrane permeable. Accordingly, further reliance on Youn fails to cure this deficiency of the cited references.

For all of these reasons, Applicant respectfully submits that the rejections of claims 1-4, 6, 9-18, 60, and 63-74 under 35 U.S.C. § 103(a) are not properly applied. Accordingly, reconsideration and withdrawal of the rejections are respectfully requested.

In view of the above remarks, reconsideration and favorable action on all claims is respectfully requested. Should any questions remain in view of this communication, the Examiner is encouraged to call the undersigned so that a prompt disposition of this application can be achieved. Please charge any additional fees, or make any credits, to Deposit Account No. 50-1355.

Respectfully submitted,

Kevin J. Forrest (Reg. No. 45,881)
FOR

Date: October 7, 2002

Lisa A. Haile, J.D., Ph.D.
Registration No.: 38,347
Telephone: (858) 677-1456
Facsimile: (858) 677-1465

USPTO CUSTOMER NUMBER 28213
GRAY CARY WARE & FREIDENRICH LLP
4365 Executive Drive, Suite 1100
San Diego, CA 92121-2133

APPENDIX: Abstract

ABSTRACT

The present invention provides methods and reagents for targeting probes to selected cellular locations, through the expression of specific binding partners to that probe within the cell. In one embodiment, the probes may comprise spectroscopic probe that can be used in a method for localizing a specific binding partner within a cell, and for creating assays for post-translational activities. The invention allows the monitoring of the location of such intracellular specific binding partners over time and in response to stimuli, such as test chemicals. The spectroscopic probes can be used for screening a test chemical for activity. The present invention also includes cells and transgenic organisms comprising the intracellular specific binding partner, wherein the specific binding partner can bind with the spectroscopic probe/ligand conjugate.